UTAH DEPARTMENT OF HEALTH

Prion Diseases (including Creutzfeldt-Jakob Disease)

Disease Plan

Quick Links:

Contents

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Questions about this disease plan?

Contact the Utah Department of Health Bureau of Epidemiology at 801-538-6191.

✓ CRITICAL CLINICIAN INFORMATION

Clinical Evidence

Signs/Symptoms

- Sporadic CJD (sCJD)
  - Dementia; early neurologic signs
  - Rapid, progressive mental deterioration
  - Myoclonus
  - Ataxia
  - Dysarthria
- Variant CJD (vCJD)
  - Early psychiatric and behavioral symptoms (depression or psychosis)
  - Painful sensory symptoms (e.g., “stickiness” of the skin)
  - Delayed onset of unsteadiness, difficulty walking, and involuntary movements
- Gerstmann-Sträussler-Scheinker Syndrome (GSS)
  - Loss of coordination, followed by dementia
- Kuru
  - Similar to GSS; loss of coordination, followed by dementia
- Fatal Insomnia (sFI)
  - Trouble sleeping, followed by insomnia and dementia
- Variably Protease-Sensitive Prionopathy
  - Dementia with prominent neuropsychiatric manifestations
  - Progressive motor decline (ataxia and/or Parkinson-like symptoms)

Period of Communicability

- There is no evidence of person-to-person transmission by casual contact.
- Brain and other neurological tissues may be infectious when handled directly throughout symptomatic illness, and possibly during later stages, but period of communicability is generally unknown.

Incubation Period

- The incubation period is unknown for the majority of prion diseases and is believed to be variable.
- vCJD: some cases have had incubation periods as short as 5-10 years.
- iCJD: The incubation period is unknown and probably depends upon the mode of transmission. One study estimated a mean time of 9-10 years based upon mathematical models of the incubation time for iCJD acquired after administration of human growth hormone in a population. However, incubation periods as short as five years, and as long as 30 years, have been reported in other patients.
- Incubation for Kuru is likely up to 50 years.

Mode of Transmission

- The mode of transmission of sCJD and sFI is unknown. It is theorized that sporadic mutations in the normal protein result in disease.
- Familial CJD (fCJD), familial FI (FFI), and GSS are caused by genetic mutations in the prion protein gene.
- Iatrogenic CJD is acquired following certain medical procedures, such as transplantation of prion-infected corneas or other tissues, the administration of hormones derived from human glands, or by contaminated neurosurgical instruments.
- vCJD in humans results from the consumption of contaminated meat or meat by-products from BSE-infected cattle.
- Person-to-person transmission of Kuru occurred through ritual practices involving cannibalism and no longer occurs in persons born after such practices were abandoned.

Laboratory Testing

Test Type

- CSF tests (14-3-3 protein assay, tau protein, RT-QuIC)
- EEG, MRI to detect abnormalities in the brain
- Tissue testing/brain biopsy
- Brain autopsy is the only definitive test to diagnose prion disease
- Immunohistochemistry
- Western Blot
- PrP gene sequencing

Type of Specimens

- Brain tissue and spinal fluid

Treatment Recommendations

Type of Treatment

- Supportive/palliative

Prophylaxis

- None

Contact Management

Isolation of Case

- None

Quarantine of Contacts

- None

Infection Control Procedures

- CDC has specific infection control recommendations for preventing transmission of CJD at http://www.cdc.gov/prions/cjd/infection-control.html.

✓ WHY ARE PRION DISEASES IMPORTANT TO PUBLIC HEALTH?

Prion diseases are a group of rare, rapidly progressive, and invariably fatal neurologic diseases characterized by an unusually long incubation period. There are five human prion diseases currently recognized. These include Kuru (first identified in the 1950's), Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD also known as new variant CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). Creutzfeldt-Jakob disease (CJD) is the most common prion disease seen in Utah and worldwide, although it is still rare. There is no cure and no vaccine to prevent prion disease. Correct diagnosis and early detection of cases are crucial in preventing potential iatrogenic exposures and identifying outbreaks and potential new variants of CJD.

✓ DISEASE AND EPIDEMIOLOGY

Clinical Description

Clinical and Pathologic Characteristics Distinguishing Classic CJD from Variant CJD		
Characteristic	**Classic CJD**	**Variant CJD**
Median age at death	65 years	26 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/ behavioral symptoms; painful dyesthesiasis; delayed neurologic signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
"Pulvinar sign" on MRI	Not reported	Present in >85% of cases
Presence of "florid plaques" on neuropathology	Rare or absent	Present in large numbers
Immunohistochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistant prion protein	Not reported	Marked accumulation of protease-resistant prion protein

Creutzfeldt-Jakob disease (CJD) is the most common of the human prion diseases, although it is still rare. Rapidly progressive mental deterioration and myoclonus are the two main clinical manifestations. Early personality changes and movement disorders, including ataxia (lack of muscle coordination) and dysarthria (difficulty in speech), are also common. Myoclonus is present in 90% of cases at some point during the illness. Sporadic or classic CJD (sCJD) develops when prion protein normally present throughout the body begins folding into an abnormal shape. This shape triggers prion proteins in the brain to assume the same abnormal shape. The presence of abnormal prion proteins in the brain causes destruction of brain cells. The processes that initiate abnormal folding of prion proteins are not well understood. Sporadic CJD accounts for about 85% of cases. Variant CJD (vCJD) is distinguished from sporadic CJD (sCJD) by a typical younger age of onset, early psychiatric and behavioral symptoms (depression or psychosis), painful sensory symptoms (e.g., “stickiness” of the skin), delayed onset of unsteadiness, difficulty walking, and involuntary movements. There is now strong evidence that the agent responsible for prion disease in cows, bovine spongiform encephalopathy (BSE or ‘mad cow disease’), is responsible for vCJD in humans. Iatrogenic CJD (iCJD) cases occurs following transplantation of tissues or pituitary hormones from a CJD patient into a normal person. Iatrogenic CJD cases also tend to be younger than sCJD cases. Familial CJD (fCJD) is a hereditary form of the disease.

Younger patients with sCJD have clinical features that are somewhat distinct from older patients. In one case study of 52 patients younger than 50 years, psychiatric symptoms were more prominent and the clinical course more prolonged than in older patients. These features may have suggested vCJD, but test results, cerebrospinal fluid (CSF) protein markers, and neuroimaging were consistent with sCJD.

A number of variants or subtypes of CJD have been defined based upon focal neurologic findings reflecting predominant involvement of individual brain regions. Examples of these include forms with mainly visual (Heidenhain variant), cerebellar (Oppenheimer-Brownell variant), thalamic, and striatal features. Variants of sCJD have also been classified based upon the genotype of the prion protein gene (PRNP) and the molecular properties of the pathological prion protein.

Gerstmann-Sträussler-Scheinker Syndrome (GSS) is characterized by the loss of coordination, often followed by dementia. It is a hereditary prion disease caused by a mutation in the prion protein.

Kuru is an acquired prion disease that is now virtually extinct. It was first described in members of a native tribe in New Guinea known to practice cannibalism. Its symptoms are similar to GSS.

Fatal Insomnia (FI) is a disease characterized by trouble sleeping, followed by insomnia and dementia. It can be sporadic (sFI) or familial (FFI).

Variably Protease-Sensitive Prionopathy is a new prion disease characterized by dementia with prominent neuropsychiatric manifestations and progressive motor decline (ataxia and/or Parkinson-like symptoms). There appears to be a genetic link, but additional research is needed.

Causative Agent

Prions are small infectious protein particles; they contain no nucleic acids. Prion diseases, also called transmissible spongiform encephalopathies (TSEs), are thought to result from the presence of abnormal prion proteins (protease-resistant prion protein, or PrP-res) that trigger chain reactions causing normal protein in the brain to change to abnormal protein. These abnormal proteins are resistant to enzymatic breakdown, and they accumulate in the brain, leading to damage. In addition to the four human prion diseases, there are five animal prion diseases. These diseases include scrapie in sheep and goats, chronic wasting disease (CWD) in deer and elk, transmissible mink encephalopathy (TME), feline spongiform encephalopathy, and bovine spongiform encephalopathy (BSE) in cows (also called “mad cow disease”).

Human TSE	First Reported
Creutzfeldt-Jakob Disease (CJD)	
Sporadic (sCJD)	**1921**
Familial (fCJD)	**1924**
Iatrogenic (iCJD)	**1974**
Variant (vCJD)	**1996**
Gerstmann-Sträussler-Scheinker Syndrome (GSS)	**1936**
Kuru	**1957**
Fatal Insomnia	
Familial (FFI)	**1986**
Sporadic (sFI)	**1998**
Variably Protease-Sensitive Prionopathy	**2008**

Table courtesy: WHO

Differential Diagnosis

CJD should be suspected in patients who present with a rapidly progressive dementia syndrome, particularly if accompanied by myoclonus, ataxia, and/or visual disturbances. There are many different conditions that cause progressive dementing disorders, the most common being Alzheimer’s disease. Other causes include, but are not limited to, vascular dementia, Lewy body disease, cerebellar degeneration, frontotemporal dementia (e.g., Pick’s disease and motor neuron disease type), progressive supranuclear palsy, multiple system atrophy, autoimmune disorders including paraneoplastic syndromes, demyelinating disease, central nervous system vasculitis, sarcoidosis, Hashimoto's encephalopathy, corticobasal degeneration, metabolic encephalopathies, drug-induced encephalopathies (e.g., bismuth, amitriptyline, mianserin, lithium, baclofen), viral encephalitis, fungal and tubercular meningitis, malignancy including lymphoma, gliomatosis cerebri, multiple cerebral abscesses, toxic encephalopathies including alcoholic cerebral degeneration and methylmalonic academia, and AIDS-dementia.

Laboratory Identification

Routine laboratory and diagnostic tests are rarely helpful in establishing a diagnosis of CJD or any other prion disease. However, these tests may be useful in the differential diagnosis. The National Prion Disease Pathology Surveillance Center (NPDPSC) at the Division of Neuropathology at Case Western Reserve University is the leading institution in the U.S. for diagnosing prion disease. It is supported by the Centers for Disease Control and Prevention (CDC). A small fee is charged for laboratory testing, but autopsy services are free of charge. If a case of CJD or any other prion disease is suspected, testing should be coordinated through NPDPSC.

14-3-3 protein assay

Elevated levels of the 14-3-3 protein in CSF have been reported as helpful in diagnosis of CJD. Ninety-five percent of patients with confirmed sCJD and 93% of patients with probable sCJD have been reported to have elevated levels of this protein. However, elevations in the protein also occur with other diseases, so a positive test should always be considered in conjunction with clinical history. A negative test does not exclude the diagnosis, especially in cases of possible fCJD or non-classical sCJD, and a positive result can occur in non-prion diseases. Elevated CSF levels of most 14-3-3 proteins are described in a variety of other conditions including Alzheimer disease, vascular dementia, metabolic and viral encephalopathies, and paraneoplastic syndromes, indicating that none of these is clearly diagnostic of prion disease. False negatives may occur in fCJD and non-classical sCJD.

Tau Protein

A positive CSF tau test can be helpful in diagnosing sCJD. The NPDPSC performs the tau protein test, along with the 14-3-3 protein test. A positive CSF test for tau protein is not a definitive diagnostic test for sCJD and must be interpreted in the context of clinical disease and pathological examination of brain tissue. Elevations in tau protein may also be found in other neurological diseases. In one large case study, tau had superior accuracy and specificity when compared to 14-3-3 protein as a diagnostic test for sCJD, although tau tests also produced a significant number of false negative and false positive results.

RT-QuIC

Prion protein diagnostic assays performed on blood samples are in development. One of these, real-time quaking-induced conversion (RT-QuIC), is an assay in which disease-associated prion protein (PrP) initiates a rapid conformational transition in recombinant PrP (recPrP), resulting in the formation of amyloid that can be monitored in real time. In one series with a validation cohort, the sensitivity and specificity of RT-QuIC were 87-91% and 98-100%, respectively. The NPDPSC now reflexively performs RT-QuIC on all CSF samples that have 14-3-3 levels of 500 pg/mL or higher.

Tissue testing

Confirmatory diagnosis of prion disease requires pathologic examination of brain tissue.

Brain biopsy

A brain biopsy may detect prion disease, but should not be used to rule it out. False negatives can occur because samples collected may not include the brain tissue where the abnormal prions are present.

Brain autopsy

A brain autopsy is the only definitive test to diagnose prion disease. In the U.S., the NPDPSC provides free autopsy services. This national reference laboratory, established by the CDC and sponsored by the American Association of Neuropathologists, provides prion disease diagnostic testing.

Immunohistochemistry

This test is run by NPDPSC on fixed brain tissue and identifies whether the specimen is positive or negative for prion disease based on immunostaining of the prion protein. When possible, it can also establish a tentative diagnosis regarding the type of prion disease.

Western Blot

This test is run by NPDPSC on frozen brain tissue and identifies whether the specimen is positive or negative for prion disease based on Western blot analysis of the tissue. When possible, it can also establish a tentative diagnosis regarding the type of prion disease.

PrP Gene Sequencing

This test is run by NPDPSC on blood or other tissues and detects the mutation in the gene which encodes the prion protein. The presence of a mutation indicates a hereditary form of CJD, FFI, or GSS.

Treatment

There is no effective treatment for CJD which is uniformly fatal. Death usually occurs within one year of symptom onset with median disease duration of six months. No treatment to date has been shown to slow or halt the disease. All treatment is supportive and palliative.

Case Fatality

The case fatality rate for any of the prion diseases is 100%. Death due to sCJD usually occurs within 3-12 months (mean of 7 months). Variant CJD has a longer clinical course of illness than sCJD (mean of 14 months). Death due to FI, Kuru, and GSS usually occur within one year, 3-12 months, and 2-6 years, respectively.

Reservoir

Humans are the only known reservoir for CJD, Kuru, GSS, and FI. The reservoir for vCJD is believed to be BSE-infected cattle. Other animals can be infected with TSEs, but it is unknown if these other TSEs are communicable to humans.

Transmission

The mode of transmission of sCJD and sFI is unknown. It is theorized that sporadic mutations in the normal protein result in disease. Familial CJD (fCJD), FFI, and GSS are caused by genetic mutations in the prion protein gene, which causes a change in the amino acid sequence of the normal prion protein. Latrogenic CJD is acquired following certain medical procedures, such as transplantation of prion-infected corneas or other tissues, the administration of hormones derived from human glands, or by contaminated neurosurgical instruments. Although not firmly established, it is believed that vCJD in humans results from the consumption of contaminated meat or meat by-products from BSE-infected cattle. Person-to-person transmission of Kuru occurred through ritual practices involving cannibalism and no longer occurs in persons born after such practices were abandoned.

Susceptibility

Published and unpublished information indicates that infectivity is found most often and in highest concentration in the central nervous system, specifically the brain, spinal cord, and eye. Persons with contact to these organs in cases with prion disease are at greatest risk for acquiring the disease. Familial prion diseases (GSS, FFI, fCJD) are caused by genetic mutations in the prion protein gene. The only persons that can acquire these forms are those that are genetically predisposed.

Incubation Period

The incubation period is unknown for the majority of prion diseases and is believed to be variable. In vCJD, some cases have had incubation periods as short as 5-10 years. The incubation period for iCJD is unknown and probably depends upon the mode of transmission. One study estimated a mean time of 9-10 years based upon mathematical models of the incubation time for iCJD acquired after administration of human growth hormone in a population. However, incubation periods as short as five years and as long as 30 years have been reported in other patients. Incubation for Kuru is likely up to 50 years.

Period of Communicability

CJD is not infectious in the usual sense; there is no evidence of person-to-person transmission by casual contact. The brain and other neurological tissues may be infectious when handled directly throughout symptomatic illness, and possibly during the later stages of the incubation period.

Epidemiology

Kuru was first identified in the 1950s in Papua, New Guinea among persons who participated in ritual mourning ceremonies involving cannibalism. It was determined that the chain of infection

started early in the 20th century, possibly with ingestion of tissue from a person with sCJD. The incidence of Kuru declined following cessation of the ceremonies. Eleven new cases were identified as recently between July 1996 and June 2014, suggesting a long incubation period. Sporadic CJD has been reported worldwide. The annual incidence rate for sCJD is approximately 1 case/1,000,000 population worldwide. The highest age-specific incidence rate (over 5 cases/1,000,000 population) occurs in those aged 65-79 years. CJD has been reported in persons aged 14-90 years, with over 95% of cases aged 35 years or older, and with the peak of disease onset occurring in the 60-90 year-old age group.

Familial CJD (fCJD) has an average age of onset that is approximately ten years younger than sCJD. GSS is an inherited fCJD with an incidence of 1-10 cases per 100 million population per year worldwide, which mainly affects cases in mid-life (mean age 43-48 years). Fatal insomnia is another type of fCJD that affects only families with the genetic anomaly. There have been about 100 cases identified worldwide. In 1998, the first sporadic case of fatal insomnia was identified in the world. Since then there have been a total of nine cases identified.

In 1996, a new form of CJD, denoted variant CJD (vCJD), was identified in the United Kingdom (U.K.). The source of vCJD is thought to be cattle with BSE on the basis of temporal association and some biochemical markers. Over 150 cases of vCJD have been reported worldwide, mainly from the U.K., France, and 10 other countries, including the U.S. Cases outside the U.K. had either consumed beef exported from the U.K., or had traveled or lived in the U.K. or a country with exported cattle or beef from the U.K.. Variant CJD typically occurs at a younger age than other human prion diseases, with disease onset peaking in the 25-29 year-old age group and with a mean age at death of 28 years (range 12-74 years). Four cases of vCJD have been identified in the U.S., three of whom had known international exposures (consumption of contaminated beef outside the U.S. in countries with known vCJD cases). But for the most recent case, identified in 2013, risk exposure is less clear; evidence indicates that exposure to contaminated beef occurred outside the U.S. more than a decade before illness onset.

Iatrogenic CJD is rare and is believed to be controlled by current medical practices. New cases are probably associated with long incubation periods from earlier exposures, such as administration of cadaveric human pituitary hormones (growth hormone and gonadotrophin), dural graft transplants, use of dural mater in radiographic embolization procedures, corneal transplants, liver transplants, the use of contaminated neurosurgical instruments or stereotactic depth electrodes, and secondary infection with vCJD through transfusion of infected blood products. Dural graft transplants and use of cadaveric pituitary hormones account for the vast majority of cases of iCJD. Iatrogenic routes for transmission have now been largely eliminated following changes in procedures used to prepare dural grafts, and use of recombinant-derived hormones rather than hormones derived from cadaveric pituitary pools. An international CJD surveillance team reported that, in 2000, all incident cases of iCJD were due to long incubation periods from infections acquired before 1985. An exception may be the use of Lyodura dural grafts; those manufactured before 1987 (before new procedures were instituted) were not recalled internationally, and continued to be used until 1993. Cases of iCJD related to these grafts continue to accrue, in some cases 25 years after surgery. In addition, there are four reported cases of transfusion-associated vCJD.

Variably protease-sensitive prionopathy is a rare, new prion disease. Only 30 cases have been reported worldwide, and all cases have a long disease duration (approximately 45 months), older age at onset (approximately 72 years), and similar clinical symptoms.

Transfusion-related CJD
No definite cases of transfusion-associated iCJD are known to have occurred, but transfusion-associated vCJD has been reported. Several cases of transfusion transmission of vCJD in the U.K. have been reported. All cases developed vCJD after receiving blood donated from a confirmed vCJD individual. Incubation was prolonged with an average of 5.5 years between transfusion and development of vCJD.

Possible animal origins of sCJD
Recent studies of bovine prion strains indicate there is more than one type of BSE. One strain of BSE is responsible for the outbreak of vCJD in Europe in the 1990's, but additional strains show similarities to sCJD PrPSc molecular signatures. However, the significance of this PrPSc molecular similarity is unclear and further studies and evidence need to be researched.

CJD is found everywhere in the world, but it is very rare. On average, only one in a million people each year will get this disease. Since 1980, 35 cases of CJD have been identified in Utah. This number is not higher than expected.

✓ PUBLIC HEALTH CONTROL MEASURES

Public Health Responsibility

- Investigate all suspect cases of disease; complete and submit appropriate disease investigation forms.
- Provide education to the general public, healthcare providers, morticians, and first responders regarding disease transmission and prevention.

Prevention

- Tissue from an infected person cannot be used in transplants or organ donation. This includes pituitary hormones (e.g., growth hormone) extracted from a person with CJD.
- EEG electrodes and surgical instruments contaminated by tissue of an infected person should be appropriately decontaminated and sterilized.
- Meat from cattle herds infected with the agent causing BSE should not be consumed.
- Meat from deer and elk infected with chronic wasting disease (CWD) should not be consumed.
- Blood donation should not be accepted from persons at high risk for vCJD. These include:
    - Persons with history of residence in, or travel to, the U.K. for three months or longer during 1980-1996, or
    - Persons traveling to other European countries for an extended period of time since 1980.

When determining risk, infectivity of a tissue must be considered, together with the route of exposure.

- **Cutaneous exposures** of intact skin or mucous membranes (except those of the eye) pose **negligible risk**; however, it is prudent and highly recommended to avoid such exposures when working with any tissues of a CJD patient (e.g., during autopsy or embalming procedures).
- **Transcutaneous exposures**, including contact exposures to non-intact skin or mucous membranes, splashes to the eye, and inoculations via needle or scalpel and other surgical instruments pose a greater **potential risk**. Thus, personal protective equipment (PPE) should be used to prevent such exposures.
- **Central nervous system (CNS) exposures** (e.g., inoculation of the eye or CNS) pose a very **serious risk**, and appropriate precautions must always be taken to avoid these types of exposures.

CDC has specific infection control recommendations for preventing transmission of CJD at http://www.cdc.gov/prions/cjd/infection-control.html.

Chemoprophylaxis

There is no chemoprophylaxis available.

Vaccine

There is no vaccine available to prevent prion disease.

Isolation and Quarantine Requirements

Isolation: None.

Quarantine: None for patient. Quarantining neurosurgical equipment used on suspect cases is recommended to prevent spread to other surgical patients.

✓ CASE INVESTIGATION

Reporting

All persons suspected to have, or diagnosed with, any prion disease should be reported to public health immediately.

Case Definition

There are currently no case definitions for prion disease. The following case classifications have been adapted from CDC and WHO diagnostic criteria.

Case Classification

Sporadic CJD (CDC 2010)

Clinical Criteria

In the absence of an alternative diagnosis, rapidly progressive dementia **and** at least two of the following:

- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

Laboratory Criteria

Confirmatory

- Standard neuropathological techniques (brain autopsy, brain biopsy, etc.), and/or
- PrP immunohistochemistry testing, and/or
- Western blot confirmed protease-resistant PrP, and/or
- Presence of scrapie-associated fibrils

Probable/presumptive

- A typical EEG (periodic sharp wave complexes) during an illness of any duration**,** and/or
- A positive 14-3-3 CSF assay in patients with a disease duration of less than two years, and/or
- High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)

Case Classification

Confirmed

A case with confirmatory laboratory results.

Probable

- A clinically compatible case with probable laboratory results, OR
- A patient with neuropsychiatric disorder plus a positive RT-QuIC in cerebrospinal fluid (CSF) or other tissues.

Suspect

A clinically compatible case, and at least one negative probable laboratory result, and a duration of illness less than two years and without routine investigations indicating an alternative diagnosis.

Classification Table I

Criteria for defining a case of Sporadic CJD

Criterion	Confirmed	Probable	Probable	Suspected
Clinical Evidence				
Neuropsychiatric disorder			N	
Rapidly progressive dementia		N		N
Myoclonus		O_1		O_1
Visual or cerebellar signs		O_1		O_1
Pyramidal/extrapyramidal signs		O_1		O_1
Akinetic mutism		O_1		O_1
Alternative diagnosis		A		A
Duration of illness less than two years				N
Laboratory Evidence				
RT-QuIC in cerebrospinal fluid (CSF) or other tissues			N	
Standard neuropathological techniques (brain autopsy, brain biopsy, etc.)	S			A_1
PrP immunohistochemistry testing	S			A_1
Western blot confirmed protease-resistant PrP	S			A_1
Presence of scrapie-associated fibrils	S			A_1
Positive typical EEG (periodic sharp wave complexes) during an illness of any duration		O		A_1
Positive 14-3-3 CSF assay in patients with a disease duration of less than two years		O		A_1
Positive MRI high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)		O		A_1

Notes:

N = All “N” criteria in the same column are Necessary to classify a case.

S = This criterion alone is Sufficient to classify a case.

O = At least one of any “O” criteria in each category (e.g., clinical presentation and laboratory findings) in the same column is required to classify a case. A number following an “O” indicates this criterion is only required for a specific disease/condition subtype (see below).

O_1 = At least two of any “O” criteria in each category (e.g., clinical presentation and laboratory findings) in the same column is required to classify a case.

A = This criterion must be absent (e.g., NOT present or a negative test result) for the case to meet the classification criteria. A number following an “A” indicates this criterion is only required for a specific disease/condition subtype (see below).

A_1 = At least one or more negative findings.

Iatrogenic CJD (CDC 2010)

Clinical Criteria
Progressive cerebellar syndrome in a recipient of cadaver-derived human pituitary growth hormone

Laboratory Criteria
A confirmed case of sporadic CJD.

Epidemiological Criteria
Recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

Case Classification

Confirmed
A clinically compatible case or a confirmed case of sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

Classification Table II
Criteria for defining a case of Iatrogenic CJD

Criterion	Confirmed	Confirmed
Clinical Evidence		
Progressive cerebellar syndrome	N	
Recipient of cadaver-derived human pituitary growth hormone or corneal graft	N	
Laboratory Evidence		
Confirmed CJD[1]		N
Epidemiological Evidence		
Recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation		N

Notes:
N = All "N" criteria in the same column are Necessary to classify a case.
[1] = See Laboratory findings for Confirmed Sporadic CJD in the table above (Classification table I).

Familial CJD* (CDC 2010)

Clinical Criteria
Neuropsychiatric disorder *plus* disease-specific PrP gene mutation.

Laboratory Criteria
A confirmed case of sporadic CJD.

Epidemiological Criteria
First degree relative with confirmed or probable CJD.

Case Classification

Confirmed
Confirmed or probable CJD plus confirmed or probable CJD in a first degree relative, or Neuropsychiatric disorder plus disease-specific PrP gene mutation.

**Includes Gerstmann-Sträussler-Scheinker disease and Fatal Familial Insomnia.*

Classification Table III
Criteria for defining a case of Familial CJD

Criterion	Confirmed	Confirmed
Clinical Evidence		
Neuropsychiatric disorder	N	
Laboratory Evidence		
Confirmed or probable CJD[1]		N
Disease-specific PrP gene mutation	N	
Epidemiological Evidence		
First degree relative with confirmed or probable CJD		N

Notes:
N = All "N" criteria in the same column are Necessary to classify a case.
[1] = See Laboratory findings for Confirmed Sporadic CJD in the table above (Classification table I).

Variant CJD (CDC 2010)

Clinical Criteria
A diagnosis of variant CJD includes a variety of psychiatric symptoms, including anxiety, apathy, delusions, depression, and withdrawal; and a variety of neurological signs, including dementia, poor coordination, myoclonus, chorea, dystonia, hyperreflexia, visual signs, ataxia, and persistent painful sensory symptoms.

Laboratory Criteria

Confirmatory
- Numerous widespread Kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum - florid plaques, AND
- Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.

Suspected
A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD. Typical bilateral pulvinar high signal on MRI scan.

Epidemiological Criteria
- No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft.
- No history of CJD in a first degree relative or prion protein gene mutation in the patient.

- History of possible exposure to bovine spongiform encephalopathy (BSE) such as residence or travel to a BSE-affected country after 1980.

Case Classification

Confirmed
A case with confirmatory laboratory testing.

Suspected
In the absence of a more likely diagnosis, a person:

- With current age or age at death <55 years, and
- Duration of illness over 6 months, and
- Early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal), and
- Dementia, and
- ≥4 month delay in the development of at least two of the following:
    - Poor coordination
    - Myoclonus
    - Chorea
    - Hyperreflexia
    - Visual signs, and
- A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD, and
- No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft, and
- No history of CJD in a first degree relative or prion protein gene mutation in the patient.

OR

In the absence of a more likely diagnosis, a person:

- With current age or age at death <55 years, and
- Duration of illness over 6 months, and
- Persistent painful sensory symptoms (frank pain and/or dysesthesia), and
- Dementia, and
- At least two of the following:
    - Poor coordination
    - Myoclonus
    - Chorea
    - Hyperreflexia
    - Visual signs, and
- A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD, and
- No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft, and
- No history of CJD in a first degree relative or prion protein gene mutation in the patient.

OR

In the absence of a more likely diagnosis, a person:

- With a progressive neuropsychiatric disorder, and
- Duration of illness over 6 months, and
- Four of the following:
    - Early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal)
    - Persistent painful sensory symptoms (frank pain and/or dysesthesia)
    - Dementia
    - Myoclonus, chorea, or dystonia
    - Ataxia, and
- A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD, and
- Typical bilateral pulvinar high signal on MRI scan, and
- No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft.

Classification Table IV

Criteria for defining a case of Variant CJD

Criterion	Confirmed	Suspected		
Clinical Presentation				
Current age or age at death <55 years		N	N	
Early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal)		N		O_2
Persistent painful sensory symptoms (frank pain and/or dysesthesia)		A	N	O_2
Progressive neuropsychiatric disorder				N
Dementia		N	N	O_2
≥4 month delay in development of neurological signs after illness onset		N		
Poor coordination		O_1	O_1	
Myoclonus		O_1	O_1	
Chorea		O_1	O_1	
Hyperreflexia		O_1	O_1	
Visual signs		O_1	O_1	
Myoclonus, chorea, or dystonia				O_2
Ataxia				O_2
Duration of illness of over 6 months		N	N	N
Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis		N	N	N
Laboratory Findings				
Numerous widespread Kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum - florid plaques	N			
Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum	N			

A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD		N	N	N
Typical bilateral pulvinar high signal on MRI scan				N
Epidemiological Risk Factors				
No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft		N	N	N
No history of CJD in a first degree relative or prion protein gene mutation in the patient		N	N	
History of possible exposure to BSE such as residence or travel to a BSE-affected country after 1980[1]		C	C	C

N = All "N" criteria in the same column are Necessary to classify a case.
O_1 = At least two of any "O" in the same column is required to classify a case.
O_2 = At least four of any "O" criteria in the same column is required to classify a case.
A = This criterion must be absent (e.g., NOT present or a negative test result) for the case to meet the classification criteria.
[1] A history of possible exposure to bovine spongiform encephalopathy (BSE) such as residence or travel to a BSE-affected country after 1980 increases the index of suspicion for a variant CJD diagnosis.

Case Investigation Process

- Notify local and state health departments immediately.
- Obtain appropriate laboratory samples and preliminary clinical and epidemiologic information.
- Identify neurosurgical or neurological medical procedures as quickly as possible after notification of a suspected case.
- Refer to CJD checklist for providers to assure proper procedures are followed (Attachment A).
- Refer to CJD checklist for local health departments (LHDs) to assure proper procedures are followed (Attachment B).

Outbreaks

Prion diseases do not cause outbreaks in the usual sense. However, if the reported incidence of disease is higher than normal, investigation will be necessary to determine if a common source is causing infection.

Identifying Case Contacts

Prevention of Iatrogenic CJD

Prion proteins cannot be inactivated by routine methods of decontamination. For any suspect cases of CJD for which a biopsy was performed, confirm with the infection control personnel that appropriate disinfection and sterilization methods were used on the neurosurgical instruments or devices as recommended by the CDC.

Case Contact Management

If iatrogenic contacts are identified, the LHD should confer with the Utah Department of Health (UDOH), who will confer with the State Epidemiologist and CDC as necessary. The necessity of contacting exposed individuals will be determined on a case-by-case basis.

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✓ VERSION CONTROL

08.15.15: Updated clinical information, epidemiology; added checklists for LHDs and providers.
10.16.17: Updated lab identification, prevention, links, and references; added Critical Clinician Information section.
01.03.20: Updated swim lanes per CDC guidance
02.25.20: Laboratory Electronic Reporting Rules

✓ UT-NEDSS Minimum/Required Fields by Tab

Demographic

- First Name
- Last Name
- Parent/Guardian
- Area Code
- Phone Number
- Date of Birth
- Birth Gender
- Race
- Ethnicity
- Street
- City
- County
- Zip
- State

Clinical

- What disease does the patient have?
- Which type?
- Admission Date
- Onset Date
- Date Diagnosed
- Hospitalized
  - Admission Date
  - Hospital Medical Record Number
- Died
  - Date of Death
  - Age at death (years)
- Pregnancy Status
- Discharge Date
- Disease
- Health Facility
- Onset Date
- Treatment
  - Treatment Given
- Did the patient see a doctor?
  - Clinician Last Name
  - Clinician First Name
  - Clinician Phone Number
- Has NPDPSC been contacted on this case?
- Has the NPDPSC paperwork been submitted to the family for consent?
  - List the date to the family:
- Has the NPDPSC paperwork been submitted to the NPDPSC?
  - List the date submitted to NPDPSC:
- Was a Magnetic Resonance Imaging (MRI) procedure performed?
  - List assessment/results
- Was an electroencephalogram (EEG) procedure performed?
  - List assessment/results
- Was a brain biopsy performed?
  - List assessment/results
- Was genetic testing for prion protein gene mutation performed?
  - List assessment/results
- Does the patient have a family history of CJD or onset of early dementia?
- Does/did the patient have persistent painful sensory symptom(s)?
- Does/did the patient have dementia?
- Does/did the patient have poor coordination/ataxia?
- Does/did the patient have myoclonus?
- Does/did the patient have chorea?
- Does/did the patient have dystonia?
- Does/did the patient have hyperreflexia?
- Does/did the patient have visual disturbances?
- Does/did the patient have field cuts?
- Does/did the patient have blindness?
- Does/did the patient have agnosia?
- At least four months after illness onset, did patient develop poor coordination?
- At least four months after illness onset, did patient develop myoclonus?
- At least four months after illness onset, did patient develop chorea?
- At least four months after illness onset, did patient develop hyperreflexia?
- At least four months after illness onset, did patient develop visual disturbances?
- Was the duration of neurological illness longer than six months in duration?

- Does/did the patient have Rapidly Progressive Dementia?
  - Onset date
- Does/did the patient have early psychiatric symptom(s)?
  - Onset date
- Apathy?
  - Onset date
- Delusions?
  - Onset date
- Depression?
  - Onset date
- Withdrawl?
  - Onset date
- Anxiety?
  - Onset date
- At any time has the patient received human pituitary growth hormone?
- At any time has the patient received dura mater graft?
- At any time has the patient received corneal graft?
- Did routine investigation of the patient indicate an alternative, non-CJD diagnosis as the etiology for the patient's symptoms?
- Did the patient donate or receive blood?
- Has the family selected a funeral home/mortuary/crematory?
- Name of funeral home/mortuary/crematory:

Laboratory

- Collection Date
- Lab
- Lab Test Date
- Was 14-3-3 protein assay done?
- Was immunohistochemistry done?
- Was Western Blot done?
- Was PrP gene sequencing done?
- Was disease?
- Organism
- Result Value
- Specimen Source
- Test Result
- Test Type
- Sent to state lab?

Epidemiological

- Healthcare Worker
- Group Living
- Occupation
- Place Exposures Type
- Place Name
- Date of Exposure
- Street
- City
- State
- County
- Zip Code
- Imported from
- Risk Factors
- Was an autopsy performed?
- Hospital where autopsy was performed:
- Age of death (years):
- Date of Autopsy:
- Was the autopsy performed by a neurosurgeon recommended by the NPDPSC?
- Autopsy Physician:
  - Physician phone number:
- Autopsy results:
- Were autopsy samples sent to the NPDPSC?
  - List date samples sent:
  - Date samples received:

Contacts

- Name
- Last Name
- First Name
- Date of Birth
- Disposition
- Disposition Date
- Contact Type
- Phone Number

Reporting

- Date first reported to public health
- Reporter Last Name
- Reporter First Name
- Phone Number
- Reporting Agency Name

Administrative

- Event Name
- Outbreak Name
- LHD Case Status
- State Case Status
- Outbreak Associated
- Outbreak Name

✓ Attachment A - CJD Checklist for Provider

Checklist for Healthcare Providers of Suspected or Probable CJD Cases

☐ Notify local or state public health department immediately if CJD, variant CJD, or other Prion disease is suspected as a cause of the patient's illness. The local public health district can assist you with many of the following tasks.

☐ Discuss autopsy with patient and/or family. The local public health district can assist you with this task if requested.

☐ Discuss genetic testing with patient and/or family. Genetic testing will identify any familial type prion disease.

- ☐ Possible referral to a genetic counselor (See http://www.nsgc.org/FindaGeneticCounselor)

☐ Possible referral to CJD Foundation for family support, including help with making decisions on autopsy. http://www.cjdfoundation.org/. The local public health district can assist you with this task if requested.

☐ The Utah Department of Health (UDOH) will contact National Prion Disease Pathology Surveillance Center (NPDPSC). The NPDPSC coordinates all autopsies, performs all testing, and assists in making a diagnosis free of charge. For autopsy support after hours and on weekends, call the NPDPSC Autopsy Line at 216-647-8148 (this number should not be used for general inquiries).

☐ Complete NPDPSC forms; forms are available online at https://case.edu/medicine/pathology/divisions/prion-center/resources-for-professionals/forms/.The local public health district can assist you with this task if requested.

- ☐ Autopsy consent form. (To be filled out by the family; 2 signature pages and 2 pages with patient information questions)
- ☐ Test request form. (Must be filled out by the physician or lab sending tissue)
- ☐ Testing and reporting form. (To be filled out by the physician; without it, a final report providing an interpretation and possible diagnosis cannot be released. Family must sign if they want genetic testing done on blood samples.)

☐ Forms should be submitted to NPDPSC and the LHD contact or the UDOH contact. They will submit the autopsy consent form to the University of Utah pathology department and to the NPDPSC for autopsy arrangements.

☐ UDOH will work with University of Utah pathology to arrange autopsy.

☐ UDOH provides requested clinical history of the patient to the NPDPSC and/or CDC.

- ☐ Summary of medical information and progress notes since the date on onset
- ☐ Information and results from EEGs and MRIs (on disk)
- ☐ Summary of relevant family history

☐ LHD or UDOH notification to funeral service director of precautions to take.

☐ Inform family of test results. The local public health district can assist you with this task if requested.

Miscellaneous Notes

- All testing and NPDPSC-approved autopsies are performed free of charge to the patient and the patient's family.
- Autopsies should ideally be done within 72 hours of death; if this cannot be achieved, then the body should be placed in refrigeration until the autopsy is performed.

✓ Attachment B - CJD Checklist for LHD

☐ Contact lab ordering physician immediately to discuss CJD potential. Verify physician has seen lab results.

☐ Review any recent surgeries case may have had and assess risk of transmission to others (type of surgery, organ donation, etc.)

☐ Educate family on CJD.

☐ Ask family what they would do if they are not able to care for the patient; e.g., care center, hospital, hospice, home health? Ensure final nursing care center knows to contact LHD or UDOH upon death of patient.

☐ Discuss autopsy with patient and/or family. The physician may have already done this; check with them and work together.

- ☐ Possible referral to CJD Foundation for family support, including help with making decisions on autopsy. http://www.cjdfoundation.org/.

☐ Work with family on mortuary choices. Contact mortuary for family if requested.

- ☐ LHD or UDOH to notify funeral service director of precautions to take.

☐ Discuss genetic testing with patient and/or family. Genetic testing will identify any familial type prion disease.

- ☐ Possible referral to a genetic counselor (see http://www.nsgc.org/FindaGeneticCounselor).

☐ The Utah Department of Health (UDOH) will contact National Prion Disease Pathology Surveillance Center (NPDPSC). The NPDPSC coordinates all autopsies, performs all testing, and assists in making a diagnosis free of charge. For autopsy support after hours and on weekends, call the NPDPSC Autopsy Line at 216-647-8148 (this number should not be used for general inquiries).

☐ Ensure NPDPSC forms are completed; they are available on-line: www.cjdsurveillance.com/index.php?page=forms

- ☐ Autopsy consent form. (To be filled out by the family; 2 signature pages and 2 pages with patient information questions)
- ☐ Test request form. (Must be filled out by the physician or lab sending tissue)
- ☐ Testing and reporting form. (To be filled out by the physician; without it a final report providing an interpretation and possible diagnosis cannot be released. Family must sign if they want genetic testing done on blood samples.)

☐ Submit completed form to the UDOH contact. They will submit the autopsy consent form to the University of Utah pathology department and the NPDPSC for autopsy arrangements.

☐ UDOH will work with University of Utah pathology to arrange autopsy and ensure paperwork has been received.

☐ UDOH provides requested clinical history of the patient to the NPDPSC and/or CDC.

- ☐ Summary of medical information and progress notes since the date on onset
- ☐ Information and results from EEGs and MRIs (on disk)
- ☐ Summary of relevant family history

☐ Stay in touch with family on weekly basis.

☐ Inform family of test results.

✓ Creutzfeldt-Jakob Disease Rules for Entering Laboratory Test Results

The following rules describe how laboratory results reported to public health should be added to new or existing events in UT-NEDSS. These rules have been developed for the automated processing of electronic laboratory reports, although they apply to manual data entry, as well.

Test-Specific Rules

Test specific rules describe what test type and test result combinations are allowed to create new morbidity events in UT-NEDSS, and what test type and test result combinations are allowed to update existing events (morbidity or contact) in UT-NEDSS.

Test Type	Test Result	Create a New Event	Update an Existing Event
14-3-3 by EIA/Elisa	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
Biopsy	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
Immunohistochemical Analysis	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
PCR/amplification	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
PrP Gene Sequencing by PCR	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
RT-QuIC	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes
Tau Protein by EIA/ELISA	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes

Western (immuno) blot	Positive	Yes	Yes
	Negative	No	Yes
	Equivocal	Yes	Yes
	Other	Yes	Yes

Whitelist Rules

Whitelist rules describe how long an existing event can have new laboratory data appended to it. If a laboratory result falls outside the whitelist rules for an existing event, it should not be added to that event, and should be evaluated to determine if a new event (CMR) should be created.

Creutzfeldt-Jakob Disease Morbidity Whitelist Rule: Never added to a new case.

Creutzfeldt-Jakob Disease Contact Whitelist Rule: Never added to contact.

Graylist Rule

We often receive laboratory results through ELR that cannot create cases, but can be useful if a case is created in the future. These laboratory results go to the graylist. The graylist rule describes how long an existing event can have an old laboratory result appended to it.

Creutzfeldt-Jakob Disease Graylist Rule: If the specimen collection date of the laboratory result is 30 days before to 7 days after the event date of the morbidity event, the laboratory result should be added to the morbidity event.

Other Electronic Laboratory Processing Rules

- If an existing event has a state case status of “not a case,” ELR will never add additional test results to that case. New labs will be evaluated to determine if a new CMR should be created.